Synthesis of Arabinofuranosyl Derivatives of 3-Deazaguanine

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Synthesis of four arabinofuranosyl derivatives of the antitumor agent 3-deazaguanine is described. By the use of ^{13}C and ^{1}H nuclear magnetic resonance spectroscopy, the structures of these nucleosides were established to be α and β pairs of N-7 and N-9 arabinosides of 3-deazaguanine. In contrast to 3-deazaguanine and its ribosyl derivative, the nucleosides described in this paper were found to be inactive against Sarcoma 180 in mice at 100 mg/kg.

Over the years, numerous analogues of naturally occurring nucleosides have been synthesized in the search for anticancer and antiviral agents. One of the interesting compounds in this category is 3-deazaguanosine [6-amino-1-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one].[1] This compound has been reported to possess a potent broad spectrum activity in vitro against various DNA and RNA viruses,[2] as well as in vivo activity against L1210 leukemia and adenocarcinoma 755 in mice.[3] A synthesis of this compound by a novel base-catalyzed ring closure of 5-(cyanomethyl)-1-(β-D-ribofuranosyl)imidazole-4-carboxamide was published recently.[1] Since the presence of the arabinofuranosyl moiety conferred antiviral properties on *ara*-A, it was considered worthwhile to synthesize 3-deazaguanosine analogues in which the ribose component is replaced by an arabinose moiety. In this paper, we report the synthesis, structural elucidation, and anticancer (S180) testing of the 7- and 9-(arabinofuranosyl) derivatives of 3-deazaguanine.

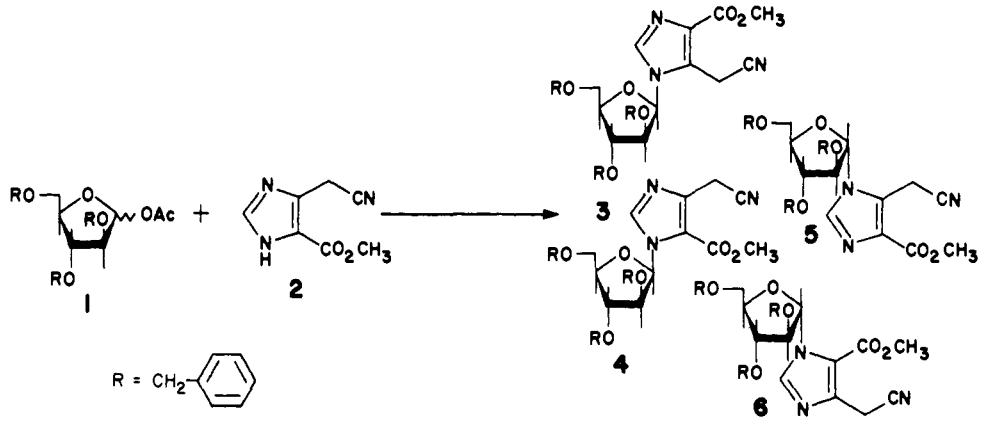
Synthesis of N-7 and N-9 Arabinofuranosyl Derivatives of 3-Deazaguanine. Synthesis of these nucleosides was patterned after the procedure used by Cook et al.[1] for the synthesis of 3-deazaguanosine. Thus, the attachment of the heterocyclic nucleus to the tri-*O*-benzylarabinofuranosyl moiety was accomplished at the imidazole **2** level (Scheme I). Four different condensation procedures were investigated. The reaction of the trimethylsilyl derivative of imidazole **2** and 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose in dichloroethane in the presence of $SnCl_4$ provided very little (TLC) condensation product. Similarly, condensation between the trimethylsilyl derivative of imidazole **2** and 1-bromo-tri-*O*-benzylarabinofuranose in acetonitrile at room temperature gave a rather poor yield of the nucleoside (~3% of the N_1 β isomer) even after 7 days. In contrast to these methods, acid-catalyzed [bis(*p*-nitrophenyl phosphate)] reaction between the free base **2** and 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose at 170 °C for 25 min produced imidazole nucleosides in about 13–18% yield. Further investigations showed that somewhat similar yields (15–25%) of the imidazole nucleosides could be realized in the above reaction even in the absence of acid catalysis. For most of the preparative purposes, therefore, the imidazole arabinosides were synthesized by the last-mentioned procedure. It should be noted that the efficiency of condensation achieved between arabinose and the imidazole **2** is generally much lower than that of the imidazole **2** with ribofuranose.[1]

The mixture of imidazole nucleosides obtained was fractionated by silica gel column chromatography. From the isolated yields of pure **3–6**, the ratio of N-1 isomer to N-3 isomer was calculated to be 1.5:1.0. Furthermore, the β anomer predominated by a ratio of at least 2.5:1 over the α anomer in each positional isomer set. Each of these imidazole nucleosides was converted into the corresponding 3-deazaguanine arabinoside by the sequence of reactions listed in Scheme II. Using compound **3** as an example, in the first reaction it was treated with liquid NH_3 at 100 °C for 90 h to provide nucleoside **7**. Under these conditions, small amounts of the ring-closed product **8** was always formed. In the initial stages of this project, nucleoside **7** was isolated on silica columns before its conversion to **8**. Later on, it was found to be more practical to treat the crude mixture of **7** and **8** with Na_2CO_3 in aqueous ethanol and purify the ring-closed product **8** by silica gel chromatography. Subsequently, the hydroxyl-protecting groups from **8** were removed by hydrogenolysis using $PdCl_2$ as catalyst.[4] The final product **9** was isolated as its hydrochloride salt. Further passage of the hydrochloride salt through a DEAE-cellulose column resulted in the free nucleoside **9**. The other 3-deazaguanine arabinosides **11**, **13**, and **15** were synthesized according to the above procedure from the corresponding imidazole arabinosides **4**, **5**, and **6** (Scheme III). In all cases, the product obtained after passage through the DEAE-cellulose column was invariably contaminated with a blue fluorescent material. Further chromatography (LC, Waters Associates, prep LC/500) provided pure crystalline compounds **9**, **11**, and **13**. However, even after several purification attempts, including LC, compound **15** could not be freed from traces of a blue fluorescent impurity.

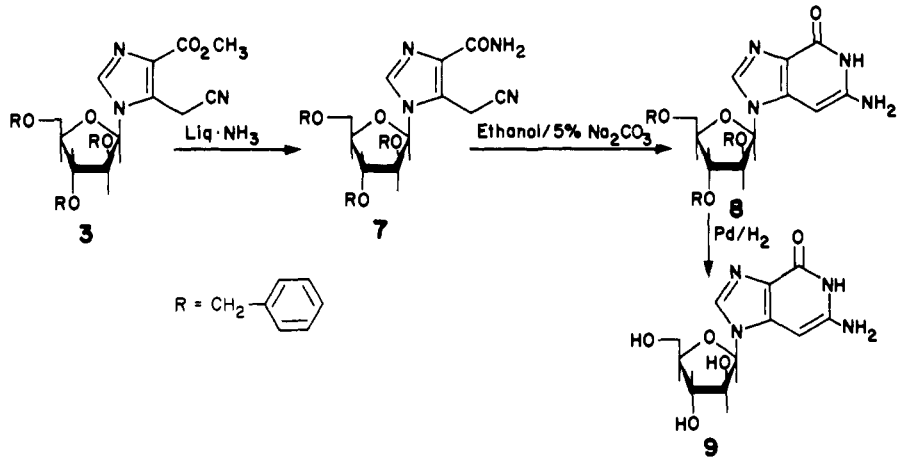
Determination of Structures. The site of N-glycosidic attachment and the anomeric configuration at C-1′ of the arabinose moiety in imidazole nucleosides **3–6** and, therefore, in 3-deazaguanine arabinosides **9**, **11**, **13**, and **15** were determined by the use of ^{13}C and ^{1}H NMR spectroscopy. By the use of ^{13}C NMR, the four imidazole nucleosides **3–6** obtained in the condensation reaction were first classified as either N-1 or N-3 glycosides. These assignments are based on the observation made in the case of several N-glycosidic site determinations in nucleosides.[5a-d] Carbon-13 chemical-shift values listed in Table I show that the signal for C-2 in all the four nucleosides **3–6** occurs about 4–6-ppm upfield as compared to the corresponding chemical shift of the imidazole base anion. Since C-2 is α to both N-1 and N-3, an upfield chemical shift of this magnitude is consistent with these expectations.[6a,b] On the other hand, C-4 is α and C-5 is β when the glycoside substituent is at N-3, and C-4 and -5 are β and α, respectively, when the sugar moiety is attached at N-1. According to the conclusions reached from ^{13}C NMR studies on *N*-alkylimidazoles[6a,b] and several nucleosides,[5] C-4 would give upfield and C-5 downfield chemical shifts in comparison to the base anion in N-3 arabinosides. An opposite result would be expected in N-1 arabinosides. Under such a comparison C-4 of compounds **3** and **5** shows a downfield shift (~3 ppm) and C-5 an upfield shift (~6 ppm). In contrast, compounds **4** and **6** give a downfield

0022-2623/79/1822-0958$01.00/0

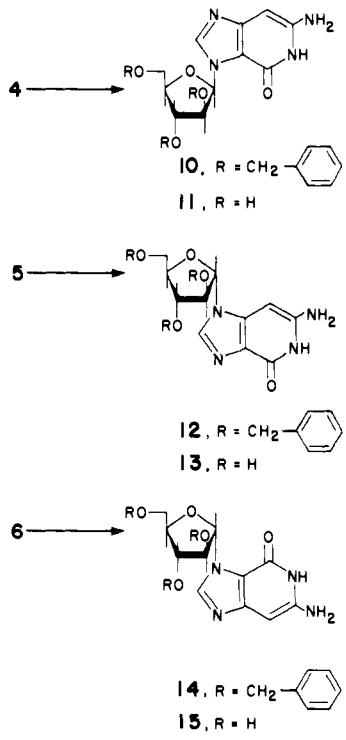
Scheme I



Scheme II

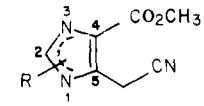


Scheme III



signal (3–4 ppm) for C-5 and an upfield signal (6–7 ppm) for C-4. These results lead to the assignment of N-1 arabinoside to **3** and **5** and N-3 arabinoside to **4** and **6**. These assignments are further supported by lower field

Table I. C-13 Spectral Chemical Shifts of Imidazole Ring Carbon Atoms[a] for the Base Anion 2 and Imidazole Arabinosides 3–6



no.	C-2[b]	C-4[b]	C-5[b]
2 (anion)	143.5	124.8	136.4
3	137.7 (136.5)	127.7 (126.8)	129.7 (129.4)
4	139.7 (136.5)	118.2 (117.8)	139.5 (138.4)
5	137.1 (136.5)	127.4 (126.8)	130.3 (129.4)
6	139.4 (136.5)	117.6 (117.8)	140.2 (138.4)

[a] The numbering of carbon atoms is maintained as shown in all of the above compounds. [b] The numbers in parentheses are the calculated values. These values are calculated according to the rules in ref 6a.

Table II. H-1′ (Anomeric Proton) Chemical Shifts and $J_{1'-2'}$ Values of Various Arabinofuranosyl Nucleosides

compd	chem shift, δ (*J*, Hz)	compd	chem shift, δ (*J*, Hz)
3 (N-1β)	6.32 (5)	**8** (N-9β)	6.08 (4.5)
5 (N-1α)	6.22 (3)	**12** (N-9α)	5.92 (3.5)
4 (N-3β)	6.56 (6)	**10** (N-7β)	6.95 (4.0)
6 (N-3α)	6.43 (0)	**14** (N-7α)	6.55 (2.5)
9 (N-9β)	5.80 (4)	**11** (N-7β)	6.66 (4.0)
13 (N-9α)	5.52[a]	**15** (N-7α)	6.18 (4.0)

[a] Due to the overlap of other signals in this region the coupling constant could not be determined.

Table III. ORD and CD Bands in Water for Arabinofuranosyl Derivatives of 3-Deazaguanine

compd	ORD λ_{max}, nm	ORD $[\phi]$, $\times 10^{-3}$	CD λ_{max}, nm	CD $[\theta]$, $\times 10^{-3}$
9 (N-9β)	589	+0.11	300	+1.23
	315 (peak)	+0.96	266	−3.28
	282 (trough)	−2.33	216	+25.21
	221 (peak)	+12.06	198	−26.31
	204 (trough)	−25.21		
13 (N-9α)	589	+0.20	327	−0.21
	314 (peak)	+2.00	266	+3.40
	304 (trough)	+1.60	221	−3.40
	290 (peak)	+2.93		
	253 (trough)	−2.27		
	203 (peak)	+18.13		
11[a] (N-7β)	589	+0.53	315	+5.45
	338 (peak)	+6.25		
	294 (trough)	−0.52	255	0.00
	228 (peak)	+27.62	220	+47.44
15[a] (N-7α)	589	+0.07	314	−1.10
	338 (trough)	−1.00	253	+1.40
	297 (peak)	+1.80	226	+6.00
	287 (trough)	+0.50		
	268 (peak)	+2.50		

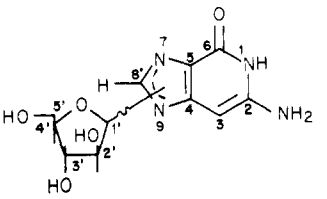
[a] These spectra were recorded in buffered aqueous solution (pH 7). Compound 15 was not analytically pure (see Experimental Section).

chemical shifts[7a-c] of the anomeric protons of 4 and 6 as compared to the corresponding signals in 3 and 5 (Table II). Similar distinction is also maintained in the ring-closed products derived from these precursors (Table II). Next, ^{1}H NMR was analyzed to establish the anomeric orientation of the N-1 and N-3 substituted arabinosides. In several examples of triazolopyrimidine nucleosides of arabinofuranose,[8] it has been shown that the anomeric proton of the β isomer always appears downfield from the anomeric proton of the corresponding α-arabinofuranoside nucleoside. As can be seen in Table II, in the N-1 arabinoside pair (3 and 5) the anomeric proton resonance of compound 3 is 0.13-ppm downfield from the corresponding signal in compound 5. Similarly, in the N-3 arabinoside pair (4 and 6), the anomeric proton signal of compound 4 occurs 0.13-ppm downfield from the signal of the anomeric proton of compound 6. On this basis, compounds 3 and 4 were assigned the β configuration and compounds 5 and 6 the α configuration. These assignments were further borne out by the chemical shifts of the anomeric protons of the cyclized products 8, 12, 10, and 14 and 9, 13, 11, 15, obtained from the imidazole precursors. Again in each pair of N-1 or N-3 glycosides, the anomeric proton signal of the β compounds 8, 10, 9, and 11 is downfield from corresponding signal of the α-compounds 12, 14, 13, and 15. Additionally, as expected, opposite Cotton effects were displayed by β and α anomers when CD/ORD spectra were run on the four 3-deazaguanine arabinosides 9, 13, 11, and 15 (Table III).

The UV data for the 3-deazaguanine arabinosides 9, 13, 11, and 15 are presented under the Experimental Section. In all cases, the UV spectral features closely resemble the data given for 3-deazaguanine ribosides,[1] thus supporting the identity of the chromophore.

The ^{13}C NMR data for the four 3-deazaguanine arabinosides (Table IV) have some interesting features. The chemical shifts of the carbohydrate moiety are similar for both β-oriented compounds 9 and 11 and differ somewhat from the corresponding signals in α-compounds 13 and 15. However, the chemical shifts of the heterocyclic moiety are affected only by the site of N attachment of the arabinose component (N-1 being different from N-3) and are virtually unchanged between α and β compounds with similar N attachment.

Table IV. C-13 Chemical Shifts of the Arabinofuranosyl Derivatives of 3-Deazaguanine[a]



carbon no.	9 (N-9β)	11 (N-7β)	13 (N-9α)	15 (N-7α)
$C_{1'}$	84.7	85.6	88.9	89.9
$C_{2'}$	74.8	75.7	74.7	75.3
$C_{3'}$	75.6	75.4	78.9	80.8
$C_{4'}$	83.8	84.2	84.5	84.8
$C_{5'}$	60.7	60.8	60.9	61.1
C_2	147.1	145.8	147.3	146.3
C_3	70.4	77.8	70.6	77.7
C_4	121.9	112.9	122.9	112.7
C_5	142.3	151.6	141.6	152.8
C_6	156.2	153.7	156.2	153.5
C_8	137.6	143.2	137.0	143.1

[a] C-13 spectra of 9-β-D- and 9-α-D-arabinofuranosyladenine[11] were used as an aid in identification of the C-13 signals of the sugar component of these compounds. The heterocycle signal assignments were based on data from imidazole precursors (Table I) and electronic considerations.

Table V. Effect of 3-Deazaguanine and its Arabinofuranosyl Derivatives against Sarcoma 180 Tumor in Mice[a]

compd	dose, mg/kg ip × 8[b]	no. of surv/no. tested	% reduct in tumor growth[c]
3-deazaguanine	100	7/16	89.6
	50	16/16	74.2
	25	16/16	78.2
	12.5	8/8	46.2
9	100	8/8	16.0
13	100	8/8	24.2
11	100	8/8	5.6
15	100	8/8	0

[a] Sarcoma 180 was induced in female CD_1 mice, 18–20 g, by the subcutaneous implantation of 3×10^7 tumor cells in the right ventrolateral area. [b] Test substances were dissolved or suspended in sterile, deionized H_2O. Treatment, 1.0 mL ip, was given shortly after implantation and once daily thereafter for a total of eight treatments. Mice were sacrificed 1 day after the last treatment. [c] An antitumor effect is defined as ≥50% reduction in tumor growth.

Biological Testing. The results of antitumor testing of the arabinofuranosyl derivatives of deazaguanine 9, 13, 11, and 15 against Sarcoma 180 in mice are presented in Table V. It can be seen that 3-deazaguanine (used as a reference standard) was active with toxicity at 100 mg/kg, active and tolerated at 50 and 25 mg/kg, and inactive at 12.5 mg/kg. All four arabinofuranosyl derivatives, however, were found to be inactive against Sarcoma 180 at the doses tested.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded in Me_2SO-d_6 on a Varian XL-100 and Brucker HFX-10 spectrometer, respectively, with tetramethylsilane as internal reference. The values are given in parts per

million (ppm) downfield from Me_4Si.

All of the arabinofuranosyl derivatives of 3-deazaguanine discussed in this paper showed sensitivity to light, although to varying degrees. Precautions, therefore, were necessary to minimize contact with light.

Methyl 5-(Cyanomethyl)-4-carboxylate (2). This compound was prepared from 4-carboxy-5-imidazoleacetamide methyl ester, which in turn was synthesized by a series of steps from 1,3-dimethyl acetonedicarboxylate according to the published procedure[9] with some minor modifications to enhance the yields of the intermediates or to economize on time. For the preparation of **2**, 8 g (4.4 mmol) of the precursor amide was heated at reflux with 50 mL of freshly distilled $POCl_3$ for 1 h. The reaction was cooled and evaporated under reduced pressure to reduce the volume to half and poured onto crushed ice (~100 g). The pH of the quenched reaction solution was adjusted to 6 by the slow addition of 28% NH_4OH with cooling. The solution was extracted with ethyl acetate (4 × 150 mL), and extracts were washed with water and dried over anhydrous Na_2SO_4. The dried ethyl acetate extract was concentrated to dryness. The residual solid (5.9 g, 70% yield) which was light yellow to tan in color was used as such for condensation experiments. However, for characterization an analytical sample was prepared by recrystallization from water, mp 170–171 °C. The NMR, UV, and infrared characteristics of this compound were found to be identical with the literature description.[9]

Condensation between Methyl 5-(Cyanomethyl)-4-carboxylate (2) and Tri-*O*-benzyl-β-D-arabinofuranosyl 1-*O*-Acetate (1). Out of several different approaches used (see Discussion) to achieve this condensation, the following method was selected as the one of choice. A mixture of **2** (9.9 g, 60 mmol) and tri-*O*-benzyl-β-D-arabinofuranosyl 1-*O*-acetate (**1**) (60 mmol) was heated in an oil bath at 190 °C under vacuum for 30 min. After the fusion mixture had cooled down to room temperature, it was dissolved in chloroform (300 mL) and washed with 5% aqueous $NaHCO_3$ (100 mL) and finally with water. The organic layer was dried over anhydrous sodium sulfate and concentrated to ~100 mL and absorbed on silica gel (silica gel 60 EM reagent) which was loaded onto a silica column (40 × 1000 mm). The column was eluted with ethyl acetate/benzene (1:1, v/v). In the first chromatography, N-1 isomers were separated from N-3 isomers. Then, N-1 isomers were fractionated on a silica column (Merck prepack column size C, eluent benzene/ethyl acetate, 1:1, v/v) to obtain N-1β, **3**, and N-1α, **5**. Similarly, N-3 isomers were chromatographed on a silica column using toluene/ethyl acetate (4:1, v/v) as eluent to obtain N-3β, **4**, and N-3α, **6** compounds. Overall yield of the nucleoside material was 15–25%. The physical data on compounds **5**, **3**, **4**, and **6** are given below.

5-(Cyanomethyl)-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-1*H*-imidazole-4-carboxylic acid methyl ester (5): obtained as an oil; NMR (Me_2SO-d_6) δ 3.64 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 6 Hz), 3.80 (s, 3, OCH_3), 4.2–4.8 (m, 11, CH_2CN, 3 × OCH_2Ph, 2′-, 3′-, and 4′-CH), 6.22 (d, 1, 1′-H, $J_{1'-2'}$ = 3 Hz), 7.1–7.5 (m, 15, 3 × CC_6H_5), 8.07 (s, 1, imidazole N=CHN). Anal. ($C_{33}H_{33}N_3O_6$) C, H, N.

5-(Cyanomethyl)-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl-1*H*-imidazole-4-carboxylic acid methyl ester (3): isolated as an oil; NMR (Me_2SO-d_6) δ 3.71 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 6 Hz), 3.80 (s, 3, OCH_3), 4.04–4.8 (m, 11, CH_2CN, 3 × OCH_2Ph, 2′-, 3′-, and 4′-CH), 6.32 (d, 1, 1′-CH, $J_{1'-2'}$ = 5 Hz), 7.0–7.45 (m, 15, 3 × CC_6H_5), 7.90 (s, 1, imidazole N=CHN). Anal. ($C_{33}H_{33}N_3O_6$) C, H, N.

5-(Cyanomethyl)-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-3*H*-imidazole-4-carboxylic acid methyl ester (4): obtained as an oil; NMR (Me_2SO-d_6) δ 3.54–3.8 (br, 2, 5′-CH_2), 3.75 (s, 3, OCH_3), 4.1–4.9 (11, CH_2CN, 3 × CH_2Ph, 2′-, 3′-, and 4′-CH), 6.56 (d, 1, 1′-CH, $J_{1'-2'}$ = 6 Hz), 6.8–7.5 (m, 15, 3 × CC_6H_5), 8.0 (s, 1, imidazole N=CHN). Anal. ($C_{33}H_{33}N_3O_6$) C, H, N.

5-(Cyanomethyl)-3-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-3*H*-imidazole-4-carboxylic acid methyl ester (6): obtained as an oil; NMR (Me_2SO-d_6) δ 3.58 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 6 Hz), 3.81 (s, 3, OCH_3), 4.0–4.85 (11, CH_2CN, 3 × CH_2Ph, 2′-, 3′-, 4′-CH), 6.44 (s, 1, 1′-CH, $J_{1'-2'}$ = 0), 7.0–7.48 (m, 15, 3 × CC_6H_5), 8.08 (s, 1, imidazole N=CHN). Pertinent ^{13}C NMR data for these isomeric imidazole nucleosides are provided in Table I. Anal. ($C_{33}H_{33}N_3O_6$) C, H, N.

9-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-3-deazaguanine (8). In addition to the synthesis of **8**, this procedure was also used for the preparation of **10**, **12**, and **14**. A sample of 1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-4-carbomethoxy-5-(cyanomethyl)imidazole **3** (5.2 g, 9.1 mmol) was dissolved in 10 mL of ethyl acetate and loaded into a steel bomb. The solvent was removed by keeping it under a vacuum at 50 °C for 18 h. In a dry box, the bomb was cooled in a dry ice–acetone bath and liquid NH_3 (~25 mL) was added to it. After sealing the bomb, the contents were heated on a steam bath for 90 h. The bomb was cooled and opened carefully, and NH_3 was allowed to escape. Final traces of NH_3 were removed under vacuum. The reaction mixture was dissolved in hot methanol, which on concentration gave a gum. From this mixture, products **7** and **8** could be separated by silica chromatography. However, for practical purposes, the gum obtained was dissolved in ethanol (25 mL) and 5% aqueous Na_2CO_3 (50 mL) and heated at reflux for 0.5 h to complete the cyclization process to **8**. The reaction solution was filtered hot and concentrated to dryness. The solid residue was taken into hot ethanol and filtered again to remove Na_2CO_3. The ethanol was evaporated and the residue dissolved in a minimum amount of ethyl acetate. The solution was loaded onto a silica column (Merck prepacked size C) and eluted with 1:1 benzene/ethyl acetate. After 700 mL of this eluent, the solvent mixture was changed to 5:1 $CHCl_3$/ethanol. On concentrating the desired fractions, compound **8** was obtained as a tan foam: yield 2.04 g (3.7 mmol), 40.5%; NMR (Me_2SO-d_6) δ 3.6 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 6 Hz), 3.8–4.6 (m, 5, OCH_2Ph, 2′-, 3′-, and 4′-CH), 4.5 and 4.6 (two s, 2 each, two OCH_2Ph), 5.4–5.6 (m, 3, =CNH_2 and =CH–), 6.0 (d, 1, 1′-CH, $J_{1'-2'}$ = 4.5 Hz), 6.8–7.6 (m, 15, CC_6H_5), 7.66 (s, 1, imidazole N=CHN), NH signal 10.5. Anal. ($C_{32}H_{32}N_4O_5$) C, H, N.

9-(2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl)-3-deazaguanine (12): obtained as a foam; yield 43%; NMR (Me_2SO-d_6) δ 3.63 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 5 Hz), 4.1–4.7 (m, 9, 3 × OCH_2Ph, 2′-, 3′-, and 4′-CH), 5.47 (s, 1, CH=CN), 5.62 (br 2, =CNH_2), 5.92 (d, 1, 1′-CH, $J_{1'-2'}$ = 3.5 Hz), 7.1–7.5 (m, 15, 3 × CC_6H_5), 7.80 (s, 1, imidazole N=CHN). Anal. ($C_{32}H_{32}N_4O_5$) C, H, N.

7-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-3-deazaguanine (10): isolated as a foam; mp 129–132 °C; yield 63%; NMR (Me_2SO-d_6) δ 3.68 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 5 Hz), 4.0–4.6 (m, 9, 3 × OCH_2Ph, 2′-, 3′-, and 4′-CH), 5.35 (br, 2, =CNH_2), 5.55 (s, 1 –CH=CN), 6.95 (d, 1, 1′-CH, $J_{1'-2'}$ = 4 Hz), 7.1–7.5 (m, 15, 3 × CC_6H_5), 8.0 (s, 1, N=CHN imidazole). Anal. ($C_{32}H_{32}N_4O_5$) C, H, N.

7-(2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl)-3-deazaguanine (14): obtained as a glassy solid; mp 59–61 °C; yield 59.5%; NMR (Me_2SO-d_6) δ 3.57 (d, 2, 5′-CH_2, $J_{4'-5'}$ = 5 Hz), 4.06–4.8 (m, 9, 3 × OCH_2Ph, 2′-, 3′-, and 4′-CH), 5.35 (br, 2, =CNH_2), 5.53 (s, 1, –CH=CN), 6.55 (d, 1, 1′-CH, $J_{1'-2'}$ = 2.5 Hz), 7.1–7.5 (m, 15, 3 × CC_6H_5), 8.06 (s, 1, N=CHN imidazole). Anal. ($C_{32}H_{32}N_4O_5$) C, H, N.

Catalytic Hydrogenolysis of the Protected 3-Deazaguanine Arabinosides.[10] The procedure described below is for the conversion of compound **8** to **9**, but other conversions, i.e., **10** to **11**, **12** to **13**, and **14** to **15**, were also performed in accordance with this method. Protected compound **8** (1.87 g, 3.3 mmol) was dissolved in methanol (75 mL) and added to a suspension of Palladium black in 200 mL of methanol (Palladium black was produced by bubbling H_2 gas into a suspension of $PdCl_2$ (1.75 g, 9.9 mmol) in methanol). Using a vibromix apparatus, hydrogen gas was bubbled into the solution for 1.75 h. The catalyst was filtered off and the methanolic solution was reduced to half of its original volume. Another 500 mL of fresh methanol was added and once more the volume was reduced to 130 mL. (This process helps in reducing the amount of dissolved HCl.) The methanolic solution was added dropwise to a large excess of ethyl acetate to precipitate the hydrochloride salt of nucleoside **9**. The precipitate was isolated and dried: yield 954 mg (91%). From 874 mg of the hydrochloride salt of **9**, 584 mg of the free nucleoside **9** was obtained by passing an aqueous solution of the salt through a DEAE-cellulose column: overall yield of **9** 68%; mp decomposes above 240 °C. NMR (Me_2SO-d_6) δ 3.5–4.2 (m, 5, 5′-CH_2, 2′-, 3′-, and 4′-CH), 5.04 (br, 1, OH), 5.4 (s, 1, –CH=CNH_2), 5.62 (br, 4, NH_2 and 2 × OH), 5.79 (d, 1, 1′-CH, $J_{1'-2'}$ = 4 Hz), 7.78 (s, 1,

N=CHN imidazole), 10.27 (br, 1, NH); UV λ_{max} (pH 1) 206 nm (ϵ 18800), 286 (13650), 315 sh (6210); UV λ_{max} (pH 7) 206 (20700), 270–271 (10980), 300 (8220); UV λ_{max} (pH 11) 205 (25000), 271–272 (10120), 300 sh (7900). Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

9-(α-D-Arabinofuranosyl)-3-deazaguanine (13): yield of the hydrochloride salt 91% and that of the free arabinoside 63%; isolated as colorless hemihydrate; mp 183–185 °C; NMR (Me_2SO-d_6) δ 3.55 (br, 2, 5′-CH_2), 4.03 (br, 2′-, 3′-, and 4′-CH), 4.32 (br, 1, 2′-CH), 4.89 (br, 1, OH), 5.49 (s, 1, –CH=CNH_2), 5.52 (due to overlap of the 1′-CH signal with olefinic proton and NH or one hydroxyl signal, the multiplicity and coupling constant could not be determined, 3 protons), 5.65 (br, 2, NH_2), 5.81 (br, 1, OH), 7.80 (s, 1, NCH=N imidazole); UV λ_{max} (pH 1) 207 nm (ϵ 19840), 286 (12380), 310 (6700); UV λ_{max} (pH 7) 205 (27200), 272 (11610), 300 (8640); UV λ_{max} (pH 11) 206 (25700), 273 (11400), 300 (8200). Anal. ($C_{11}H_{14}N_4O_5 \cdot 0.5H_2O$) C, H, N.

7-(β-D-Arabinofuranosyl)-3-deazaguanine (11). The recovery of the free nucleoside after passage through the DEAE-cellulose column was 62%. However, this material was contaminated with a blue fluorescent impurity. On further chromatography on a high performance silica column (Waters Associates, prep LC/500, using 2-propanol with 2% concentrated NH_4OH as eluent) pure material was obtained. Recrystallization from water gave a light-tan crystalline product: yield 17.4%; mp 178–180 °C; NMR (Me_2SO-d_6) δ 3.5–3.8 (m, 3, 5′-CH_2 and 4′-CH), 3.9–4.1 (m, 2, 2′- and 3′-CH), 5.04 (m, 1, OH), 5.24 (br, 2, NH_2), 5.41 and 5.47 (br, 2, 2 × OH), 5.50 (s, 1, –CH=CN), 6.66 (d, 1′-CH, $J_{1'-2'}$ = 4 Hz), 8.03 (s, 1, NCH=N imidazole), 10.46 (br, 1, NH); UV λ_{max} (pH 1) 207 nm (ϵ 20550), 278 (10920), 317 (5650); UV λ_{max} (pH 7) 216 (24200), 259–260 (5750), 318–319 (6900); UV λ_{max} (pH 11) 216–217 (24350), 259–260 (5620), 314–315 (5620). Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

7-(α-D-Arabinofuranosyl)-3-deazaguanine (15). In contrast to the preparations of compounds **9**, 11, and **13**, the N-7 substituted 3-deazaguanine arabinoside **15** presented difficulties. The reduction of its protected precursor **14** proceeded as expected to give the hydrochloride salt of **15** in 89% yield. On conversion to the free nucleoside by passage through DEAE-cellulose, the material (~66% yield) showed a contaminating blue fluorescent impurity (TLC). Several attempts on LC as in case of compound 11 failed to give analytically pure material. Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 4.99; N, 19.85. Found: C, 46.79; H, 5.29; N, 17.96. Surprisingly, the NMR spectrum of this material showed acceptable agreement with the structure and did not reveal the presence of any impurity: NMR (Me_2SO-d_6) δ 3.55 (m, 2, 5′-CH_2), 3.93, 4.13, and 4.42 (3 multiplets, 1 each, 4′-, 3′-, and 2′-CH), 4.81 (br, 1, OH), 5.34 (br, 2, NH_2), 5.43 (m, 1, OH), 5.53 (s, 1, –CH=CN), 5.72 (d, 1, OH), 6.18 (d, 1, 1′-CH, $J_{1'-2'}$ = 4 Hz), 8.13 (s, 1, N=CHN imidazole); UV λ_{max} (pH 1) 207 nm (ϵ 19000), 276–277 (9850), 318 (5500); UV λ_{max} (pH 7) 217 (21800), 258 (5600), 317–318 (6700); UV λ_{max} (pH 11) 216–217 (22190), 258–259 (5280), 315–316 (6040). The ^{13}C NMR data for the four 3-deazaguanine arabinosides **9**, 11, **13**, and **15** can be found in Table IV.

Acknowledgment. We express our thanks to Dr. T. Williams and associates (for ^{13}C and ^1H nuclear magnetic resonance), Dr. Toome (for UV and ORD/CD), Dr. Scheidl (for microchemistry), Mr. S. Traiman (for IR), and Dr. A. Cook (for helpful discussions).

References and Notes

(1) P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, Jr., and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976). For synthesis of more derivatives of 3-deazaguanosine, see P. D. Cook and R. K. Robins, *J. Org. Chem.*, **43**, 289 (1977).
(2) L. B. Allen, J. H. Huffman, P. D. Cook, R. B. Meyer, Jr., R. K. Robins, and R. W. Sidwell, *Antimicrob. Agents Chemother.*, **12**, 114 (1977).
(3) T. A. Khwaja, L. Kigwana, R. B. Meyer, Jr., and R. K. Robins, *Proc. Am. Assoc. Cancer Res.*, **16**, 162 (1975).
(4) The presence of acid was found to be essential in these hydrogenolysis reactions. This was shown by experiments in which the HCl generated by reduction of $PdCl_2$ was removed by multiple washings in methanol to avoid the formation of the hydrochloride salt of the deprotected nucleoside. Thus, completely devoid of HCl, these reactions gave no deprotected product on treatment with hydrogen.
(5) (a) G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894 (1972); (b) G. L. Szekers, R. K. Robins, P. Dea, M. P. Schweizer, and R. A. Long, *J. Org. Chem.*, **38**, 3277 (1973); (c) T. C. Thurber, R. J. Pugmire, and L. B. Townsend, *J. Heterocycl. Chem.*, 11, 645 (1974); (d) R. A. Earl, R. J. Pugmire, G. P. Revanker, and L. B. Townsend, *J. Org. Chem.*, **40**, 1823 (1975).
(6) (a) R. J. Pugmire, D. M. Grant, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.*, **95**, 2791 (1973); (b) C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *J. Med. Chem.*, **15**, 883 (1972).
(7) (a) P. Dea, G. R. Revanker, R. L. Tolman, M. P. Schweizer, and R. K. Robins, *J. Org. Chem.*, **39**, 3226 (1974); (b) S. R. Naik, J. T. Witkowski, and R. K. Robins, *J. Heterocycl. Chem.*, 11, 57 (1974); (c) G. R. Revanker and L. B. Townsend, *ibid.*, **7**, 1329 (1970).
(8) C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *J. Med. Chem.*, **15**, 883 (1972).
(9) R. K. Robins, J. H. Horner, C. V. Greco, C. W. Noell, and C. G. Bearnes, Jr., *J. Org. Chem.*, **28**, 3041 (1963).
(10) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).
(11) L. F. Johnson and W. C. Jankowski, "C-13 NMR Spectra", Wiley-Interscience, New York, 1972.

Synthesis and Antiestrogenic Activity of [3,4-Dihydro-2-(4-methoxyphenyl)-1-naphthalenyl][4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]methanone, Methanesulfonic Acid Salt

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Acylation of the sodio anion of β-tetralone with phenyl anisoate, followed by a Grignard reaction of the resultant **4** with 4-methoxyphenylmagnesium bromide, gave rise to two novel dihydronaphthalene isomers **5** and **6**. Regioselective demethylation of either **5** or **6** by NaSEt produced [3,4-dihydro-2-(4-methoxyphenyl)-1-naphthalenyl](4-hydroxyphenyl)methanone (**7**). Etherification of the phenolic group of **7** by *N*-(2-chloroethyl)pyrrolidine and subsequent methanesulfonate salt formation provided [3,4-dihydro-2-(4-methoxyphenyl)-1-naphthalenyl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone, methane sulfonic acid salt (**3**). Potent antiestrogenic activity of **3** was demonstrated by both oral and subcutaneous administration to rats and mice. In vitro binding studies with rat uterine cytosol estrogen receptors indicate compound **3** has a very high binding affinity which exceeds that of estradiol.

Triarylethylene-derived compounds of general structures 1 and 2 and their ring-oxygenated counterparts have proven for many years an unusually rich source of antiestrogenic agents.[1] More recently, certain of these com-

0022-2623/79/1822-0962$01.00/0